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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,627	12/10/2001	Emil Wei-Ming Fu	4-31692A	4092

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,627	FU ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 18, 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities:

> Throughout the specification, the recitation of the term "inverse" is indefinite because the scope of the definition of the term "inverse" is not clear. The specification does not appear to resolve how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse," dictionary or otherwise, applies to the concept of a "qualitative mass shift."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 23, 35 and 47, the recitation of "inverse labeling pattern" is indefinite because the scope of the definition of the term "inverse" is not clear in both Applicants' specification and Applicants' clarifying remarks. Both Applicants' specification and Applicants' clarifying remarks do not appear to resolve how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse," dictionary or otherwise, applies to the concept of a "qualitative mass shift."

Claim Rejections - 35 USC § 102

Claims 1-12, 14, 16-19, 21-22 and 47-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Chait *et al.* (US 6,391,649).

Chait *et al.* describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of $CLN2^+$ plus 1 mL of ^{15}N-labeled extract of $clin2^-$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^-$ plus 1 mL of ^{15}N-labeled extract of $CLN2^+$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

With respect to claims 2, 14 and 28, Chait *et al.* describe a method further comprising the step of enzymatically or chemically cleaving the labeled proteins (see col. 12, line 67, "trypsin solution").

With respect to claims 3-6 and 11-12, Chait *et al.* describe a method further comprising the step of detecting and sequencing the peptides with MS/MS (see col. 15, lines 38-41).

With respect to claims 7-10 and 15, Chait *et al.* describe a method further comprising the step of separating the labeled proteins with RP-HPLC (see col, 12, lines 26-28).

With respect to claims 14, Chait *et al.* describe a method further comprising the step of subjecting the samples to at least one fractionation technique (see col. 17, line 12, "pelleted, washed").

With respect to claims 17-19, Chait *et al.* describe a method wherein the proteins are labeled with ^{18}O isotope (see col. 5, line 55).

With respect to claims 49, Chait *et al.* describe a method wherein the assimilable source is an ammonium salt (see col. 9, line 65).

Claim Rejections - 35 USC § 103

Claims 23-28, 30, 32-40, 42 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer *et al.*, 17 ELECTROPHORESIS 945 (1996) in view of Chait *et al.* (US 6,391,649).

Schnolzer *et al.* teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see p. 950, col. 2, first full paragraph, line 2), proteolyzing each protein pool with isotopically labeled water (see p. 950, col. 2, first full paragraph, line 3), combining the protein pools (see p. 950, col. 2, first full paragraph, line 2), detecting the labeled peptides (see p. 950, col. 2, first full paragraph, lines 15-17), and comparing the labeling pattern (see p. 950, col. 2, first full paragraph, lines 6-8).

Schnolzer *et al.* do not teach a method for identifying differentially expressed protein in two different protein samples.

However, Chait *et al.* describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the

isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled (^{14}N) extract of $CLN2^{+}$ plus 1 mL of ^{15}N-labeled extract of $clin2^{-}$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^{-}$ plus 1 mL of ^{15}N-labeled extract of $CLN2^{+}$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Schnolzer *et al.*, to identifying differentially expressed protein in two different protein samples because Chait *et al.* discovered a method for analyzing post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g. drugs, hormones, etc.) in two or more biological samples (see col. 3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). In addition, Chait *et al.* discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).

With respect to claim 35, step (c), Schnolzer *et al.* teach a method wherein "peptide products continue to interact with these proteases and undergo repeated binding/hydrolysis cycles, resulting in complete equilibrium of both oxygens in the carboxy terminus of the fragment with oxygen from solvent water" (see Abstract).

Claims 13, 15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold *et al.* (US 6,670,194) in view of Chait *et al.* (US 6,391,649).

Aebersold *et al.* teach a method of identifying proteins in a sample comprising the steps of: providing two equal protein pools (see col. 5, lines 61-66), labeling each protein pool with a isotopically different labeling reagent (see col. 5, lines 61-66), combining the protein pools (see col. 6, lines 2-3), detecting the labeled peptides (see col. 6, line 9), and comparing the labeling pattern (see col. 6, lines 13). With respect to claims 13 and 15, Aebersold *et al.* teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a). With respect to claim 20, Aebersold *et al.* describe a labeling reagent containing an affinity tag (see Abstract).

Aebersold *et al.* do not provide two protein pools from each of a reference and an experimental sample.

However, Chait *et al.* describe a method for identifying a differentially expressed protein in two different samples (see Abstract, "comparing the levels of cellular components, such as proteins, present in samples which differ in some respect from each other") comprising the steps of: providing two equal protein pools (see col. 11, lines 56-57, "high abundance proteins derived from two pools") from each of a reference sample (see col. 12, lines 11-12, "expressing population is designated 'CLN2+'") and an experimental sample (see col. 12, lines 12-13, "non-expressing population is designated 'cln2-'"), labeling the protein pools with a substantially chemically identical isotopically different protein labeling reagent for proteins, wherein one pool from each of the reference and experimental pools is labeled with an isotopically heavy protein labeling reagent to provide an isotopically heavy-labeled reference pool and an isotopically heavy-labeled experimental pool, and wherein the remaining reference and experimental pools are labeled with an isotopically light protein labeling reagent to provide an isotopically light-labeled reference pool and an isotopically light-labeled experimental pool (see col. 12, lines 14-18), combining the isotopically light labeled reference pool with the isotopically heavy-labeled experimental pool to provide a first protein mixture (see col. 12, lines 16-18, "A second combined sample contained 1 mL of unlabeled

(^{14}N) extract of $CLN2^{+}$ plus 1 mL of ^{15}N-labeled extract of $clin2^{-}$"), combining the isotopically heavy-labeled reference pool with the isotopically light-labeled experimental pool to provide a second protein mixture (see col. 12, lines 14-16, "A first combined sample contained 1 mL of unlabeled (^{14}N) extract of $cln2^{-}$ plus 1 mL of ^{15}N-labeled extract of $CLN2^{+}$"), detecting the labeled proteins from each of the two mixtures (see col. 13, lines 14-15, "Mass spectrum measurements were obtained"), comparing the labeling pattern (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), wherein an inverse labeling pattern is indicative of the differentially expressed protein (see Table IV).

Therefore, it would have been obvious for a person of ordinary skill in the art to perform the method of identifying proteins in a sample, as taught by Aebersold *et al.*, by providing two protein pools from each of a reference and an experimental sample because Chait *et al.* discovered that differentially expressed proteins can be analyzed for post-translational modifications (see col. 4, lines 11-14) to analyze the effects of environmental stimuli (e.g. drugs, hormones, etc.) on two or more biological samples (see col. 3, lines 47-60) in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). In addition, Chait *et al.* discovered a method to ensure that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).

Claims 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer *et al.*, 17 ELECTROPHORESIS 945 (1996) and Chait *et al.* (US 6,391,649) as applied to claim 23, and further in view of Aebersold *et al.* (US 6,670,194).

Schnolzer *et al.* and Chait *et al.* describe a method for identifying a differentially expressed protein as substantially described supra. The aforementioned references do not teach a fractionation step prior to step (a).

However, Aebersold *et al.* teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a) as a preparative step in the analysis of membrane proteins (see col. 17, line 28). Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method of identifying differentially expressed proteins, as taught by Schnolzer *et al.* and Chait *et al.*, with a fractionation step prior to step (a) because Aebersold *et al.* discovered that panning and labeling membrane proteins with isotopic affinity tags can be used to identify important diagnostic or therapeutic targets (see col. 17, lines 49-52) without the step of solubilizing membrane proteins prior to analysis, thus avoiding a major complication facing prior art methods which require solubilization of membrane proteins prior to analysis.

Claims 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schnolzer *et al.*, 17 ELECTROPHORESIS 945 (1996) and Chait *et al.* (US 6,391,649) as applied to claim 35, and further in view of Aebersold *et al.* (US 6,670,194).

Schnolzer *et al.* and Chait *et al.* describe a method for identifying a differentially expressed protein as substantially described supra. The aforementioned references do not teach a fractionation step prior to step (a).

However, Aebersold *et al.* teach an affinity chromatographic fractionation of proteins (see e.g. col. 17, line 49, "panning") prior to step (a) as a preparative step in the analysis of membrane proteins (see col. 17, line 28). Therefore, it would have been obvious for a person of ordinary skill in the art to practice the method of identifying differentially expressed proteins, as taught by Schnolzer *et al.* and Chait *et al.*, with a fractionation step prior to step (a) because Aebersold *et al.* discovered that panning and labeling membrane proteins with isotopic affinity tags can be used to identify important diagnostic or therapeutic

targets (see col. 17, lines 49-52) without the step of solubilizing membrane proteins prior to analysis, thus avoiding a major complication facing prior art methods which require solubilization of membrane proteins prior to analysis.

Response to Arguments

In prior Office Action, claims 1-49 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitations of "equal protein pools", "proteolyzing... with isotopically labeled water" and "labeling each peptide pool with isotopically labeled water". In addition, claim 23 was rejected under 35 U.S.C. 112, second paragraph, because the phrase "during labeling" lacks antecedent basis. Applicants' claim amendments and/or related argumentation are fully persuasive and sufficient to overcome these rejections. Accordingly, these rejections are withdrawn.

In prior Office Action, Examiner objected to the specification for recitation of the term "inverse". In addition, claims 1-49 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "inverse labeling pattern". Specifically, how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern" or how the definition of the term "inverse," dictionary or otherwise, applies to the concept of a "qualitative mass shift" is not clear.

In response, Applicants appear to set forth a conditional relationship:

("isotope peak intensity ratio reversal" = 1:0 or 0:1) → ("qualitative mass shift" = "isotope peak intensity ratio reversal")

wherein the definition of "qualitative mass shift" is conditioned upon the existence of an "isotope peak intensity ratio" of 1:0 or 0:1.

Examiner observes that Applicants' specification does not appear to describe the conditional relationship, set forth *supra*. Whether persons skilled in the art would recognize the conditional relationship between the definitions of "qualitative mass shift" and "isotope peak intensity ratio reversal", or whether persons

skilled in the art would recognize that a "qualitative mass shift" species belongs to a broader genus of "isotope peak intensity ratio reversal" is not clear. Absent objective evidence to the contrary, Examiner posits that persons skilled in the art would not readily recognize such a conditioned genus-species relationship between the concepts of "isotope peak intensity ratio reversal" and "qualitative mass shift", respectively. Thus, absent objective evidence to the contrary, Examiner posits that persons skilled in the art would not readily recognize how a "qualitative mass shift" amounts to the creation of an "inverse labeling pattern", thereby rendering the scope of the term "inverse labeling pattern" wholly indefinite.

In prior Office Action, claims 1-49 were rejected under 35 U.S.C. 102(e) or 35 U.S.C. 103(a) in view of the teachings from Chait *et al.* (US 6,391,649) and Aebersold *et al.* (US 6,670,194). In response, Applicants argue:

> 1) neither Aebersold *et al.* nor Chait *et al.* teach or specifically suggest comparing the labeling patterns obtained from two experiments as is set forth in step (f) of Claim 1, 2) nor do these references teach or specifically suggest that an inverse labeling pattern, a reversal in the signal intensity ratio of the isotopic pairs of a protein between the first experiment and the second experiment, is indicative of a differentially expressed protein, and 3) that one skilled in the art would not be motivated to combine Aebersold *et al.* with Chait *et al.*, specifically Example 2, the combination of Aebersold *et al.* and Chait *et al.* does not make obvious Claims 13, 15 and 20 which depend from amended independent Claim 1.

With respect to item 1), Applicants' argument is not persuasive because Chait *et al.* teach the step of comparing labeling patterns obtained from a first experiment (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), then repeating the step of comparing labeling patterns with a second experiment (see e.g., col. 8, lines 63-64, "the process... is preferably repeated with the other cell pool"), to validate the labeling patterns obtained from a first experiment. Chait *et al.* perform these two experiments for the same reasons as Applicants: to identify labeling patterns indicative of differentially expressed proteins (see Table IV).

With respect to item 2), Applicants' argument is not persuasive because a reversal in the signal intensity ratio of the isotopic pairs of a protein between the first experiment and the second experiment inherently results from the method of Chait *et al.* when performing the steps of combining an isotopically light labeled reference pool with an isotopically heavy-labeled experimental pool in a first experiment, then combining an isotopically heavy-labeled reference pool with an isotopically light-labeled experimental pool in a second experiment. This inherently outcome of the method of Chait *et al.* would be so recognized by persons of ordinary skill.

With respect to item 3), Applicants' argument is not persuasive because the combined teachings of Aebersold *et al.* and Chait *et al.* describe all the steps of Applicants' invention, as claimed. Aebersold *et al.* teach the step of using affinity fractionation tags (see col. 5, lines 61-66), while Chait *et al.* teach the step of comparing labeling patterns obtained from a first experiment (see col. 14, lines 1-3, "comparing the sum of the intensities of the isotopically resolved components of the unlabeled peptide with the corresponding sum from the ^{15}N peptide"), then repeating the step of comparing labeling patterns with a second experiment (see e.g., col. 8, lines 63-64, "the process... is preferably repeated with the other cell pool"), to validate the labeling patterns obtained from a first experiment. Chait *et al.* provide motivation to combine the two teachings by discovering the use of two or more biological samples (see col. 3, lines 47-60) to analyze the effects of post-translational modifications (see col. 4, lines 11-14) and environmental stimuli (e.g. drugs, hormones, etc.), and in order to gain insight into mechanisms of drug action, viral infection, etc. (see col. 1, lines 28-54). Persons of ordinary skill in the art may recognize a reasonable expectation of success in combining the teachings of Aebersold *et al.* and Chait *et al.* because the method of Chait *et al.* ensures that any change in isotopic ratios is not caused by the isotopic enrichment itself (see col. 8, lines 61-64).

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

LONG V. LE
SUPERVISORY PATENT EXAMINER
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12/27/05